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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/680,514	10/06/2000	Haruhiko Yokoi	249-118	9035

7590 06/21/2002

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[REDACTED] EXAMINER

SPECTOR, LORRAINE

[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1647

DATE MAILED: 06/21/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.



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EXAMINER

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DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

- Responsive to communication(s) filed on _____
 This action is FINAL.
 Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- Claim(s) 10-18 is/are pending in the application.
Of the above, claim(s) 16-18 is/are withdrawn from consideration.
 Claim(s) _____ is/are allowed.
 Claim(s) 10-15 is/are rejected.
 Claim(s) _____ is/are objected to.
 Claim(s) 10-18 are subject to restriction or election requirement.

Application Papers

- See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
 The drawing(s) filed on _____ is/are objected to by the Examiner.
 The proposed drawing correction, filed on _____ is approved disapproved.
 The specification is objected to by the Examiner.
 The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 All Some* None of the CERTIFIED copies of the priority documents have been
 received.
 received in Application No. (Series Code/Serial Number) 08/765337.
 received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- Notice of Reference Cited, PTO-892
 Information Disclosure Statement(s), PTO-1449, Paper No(s). 3
 Interview Summary, PTO-413
 Notice of Draftsperson's Patent Drawing Review, PTO-948
 Notice of Informal Patent Application, PTO-152

-SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Part III: Detailed Office Action

Notice: Effective June 18, 2000, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit **1647**.

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Restriction Requirement:

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 10-15, drawn to fusion proteins and compositions thereof, classified in class 435, subclass 69.7, for example.
- 10 II. Claims 16-18, drawn to methods of treatment using fusion proteins, classified in class 424, subclass 192.1.

The inventions are distinct, each from the other because:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the products may be used in *in vitro* procedures, or as diagnostic reagents.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation between Examiner Sarada Prasad and Attorney Arthur Crawford on or about March 15, 2002 a provisional election was made with traverse to prosecute the invention of group I, claims 10-15. Affirmation of this election must be made by applicant in replying to this Office action. Claims 16-18 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently

named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(l).

5 **Formal Matters:**

The disclosure is objected to because of the following informalities: The priority claim introduced in the amendment filed 10/6/00 lists an incorrect serial number. The correct number is 08/765337.

Appropriate correction is required.

10

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15 Claims 10-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite because it is not clear what is intended by the negative limitation that the claimed protein has "no mouse IL-3 activity". Although the attorney, in the amendment filed 20 1/12/01 (paper number 2) states that "This is an inherent property of the fusion protein and is illustrated in the examples at page 50 and 51", the metes and terms of this limitation are not clear, and are not defined in the specification as originally filed. Amendment of the claims to indicate how such is measured, e.g. "as measured by inability to stimulate growth of Ba/F3 cells", would be remedial.

25 Claim 10 is further indefinite as it is not clear whether the entire fusion polypeptide, or only the c-mpl ligand portion thereof, is encoded by SEQ ID NO: 4, 6 or 8. In the event that the former interpretation is what is intended, claim 11 does not further limit claim 10, as the spacer peptide is inherent to all three sequences.

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

5 The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

10 (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15 This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20 Claims 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtis et al., U.S. Patent Number 5,073,627 in view of Yamasaki et al., EP 0 335 423, de Sauvage et al., Nature 369:533-538, cited by applicants, and Souza, U.S. Patent Number 4,999,291.

25 The claims are drawn to fusion proteins comprising, in amino to carboxyl terminal order, human TPO (mpl ligand) residues 1-153, a linker of varying length, and a derivative of human G-CSF.

30 Curtis et al. teach chimeric proteins in which IL-3 is fused to GM-CSF. The particular proteins were chosen for the fusion because "they have considerable overlap in their broad range of biological activities" (column 1, lines 27-29, specifically that they are both hematopoietic proteins. Curtis et al. also teach the use of a linker molecule between the two hematopoietic factors (col. 3 lines 64-65, for example), and at column 6, second full paragraph specifically teach the use of linkers

of any length effective to adopt a flexible extended conformation that does not develop an ordered secondary structure which could interfere with the functional domains of the protein, including “Virtually any permutation of amino acid sequences containing Gly, Asn and Ser”. Specifically exemplified in Figure 1 is a protein with a Gly-Ser linker sequence. Curtis et al. do not teach a fusion of G-CSF to thrombopoietin, a.k.a. mpl ligand.

Yamasaki et al. teach modified forms of G-CSF. At page 3, they disclose that the modified forms show “excellent stability and a long life in the blood” (line 9), and that the modified G-CSF “says longer in blood and stable during and/or after lyophilization than the unmodified polypeptide” (lines 11-12). One of the included derivatives, column k) of Table 1b, exactly matches that of the claimed invention. At page 6, they disclose that the protein of the invention is modified to comprise 1-3 molecules of a polyethylene glycol (PEG) derivative.

de Sauvage et al., cited by applicants, teach that mpl ligand stimulates megakaryocytopoiesis and thrombopoiesis (growth and differentiation of hematopoietic stem cells), see title. The full sequence of the human protein and nucleic acid encoding such are shown in Figure 3a, and similarity to erythropoietin (EPO) is shown in figure 3b. At page 538, de Sauvage et al. disclose that a truncated form of the protein consisting of amino acids 1-153 only retains full biological activity.

Souza, in a patent claiming recombinant production of human G-CSF, discloses that it is desirable to co-administer G-CSF “in combination with other hematopoietic factors or drugs in the treatment of hematopoietic disorders”; see column 4, lines 52-55.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the mpl ligand taught by de Sauvage et al. and the G-CSF analog taught by Yamasaki et al. in the fusion protein taught by Curtis et al. to obtain a bifunctional hematopoietic protein, and to make pharmaceutical compositions comprising such to be used for its known and expected properties. The ordinary artisan would have been motivated to do so in view of Curtis’ teachings that it is desirable to combine such activities, as well as by Souza’s teaching of combining G-CSF activity with other hematopoietic factors. The ordinary artisan would have expected the resultant fusion protein to be at least as effective as the two cytokines administered together as a

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composition. Accordingly, the invention, taken as whole, is *prima facie* obvious over the prior art.

Advisory Information:

5 No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

10 If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

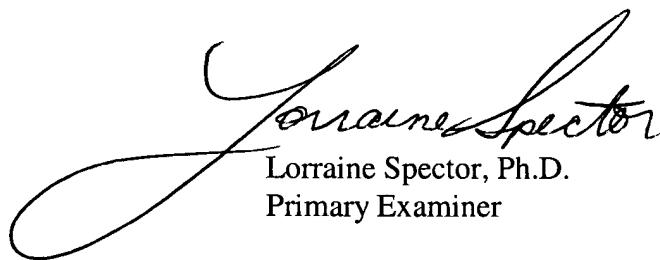
15 Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

20 Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.

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Lorraine Spector, Ph.D.
Primary Examiner

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